Elmore, Craig & Vanstone

Strategic Intellectual Property

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Date: June 28, 2005

To Examiner : **Mina Haghighatian**
Group 1616

From: Carolyn S. Elmore, Esq.
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Subject:

Paper:	Appeal Brief
Docket No.:	2685.2030-000 (US)
Appellants:	Jennifer L. Schmitke *et al.*
Serial No.:	09/888,126
Filing Date:	June 22, 2001

Number of pages including this cover sheet 31

Please confirm receipt of facsimile: **Yes** X **No** _____

Comments:

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DOCKET NO. 2685.2030-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jennifer L. Schmitke, Donghao Chen, Richard P. Batycky, David A. Edwards and Jeffrey S. Hrkach		
Application No.:	09/888,126	Group:	1616
Filed:	June 22, 2001	Examiner:	Mina Haghighatian
Confirmation No.:	9053		

For: PARTICLES FOR INHALATION HAVING RAPID RELEASE PROPERTIES

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RACHEL MEEHAN
Typed or printed name of person signing certificate

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an Appeal Brief for filing in the above-identified application.

[ ] Small entity status of this application under 37 C.F.R. 1.9 and 1.27 has been established by a Small Entity Statement previously submitted.

[ ] A Small Entity Statement to establish small entity status under 37 C.F.R. 1.9 and 1.27 is enclosed.

The fee has been calculated as shown below:

	(COL. 1)		(COL. 2)	(COL. 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDIT. FEE		RATE	ADDIT. FEE
TOTAL	57	MINUS *	60	0	X $ 9	$0	X	$18	$0
INDEP	3	MINUS **	3	0	X $42	$0	X	$84	$0
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+ $145	$0	+	$290	$0
* not fewer than 20 ** not fewer than 3					TOTAL =	$ 0	TOTAL =		$

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	[ ]	Petition for [ ] month Extension of Time	$	
	[ ]	Amendment Fee	$	
	[X]	Other Fees:		
		Appeal Brief	$	500
			$	
		TOTAL:	$	500

A check is enclosed in payment of the following fees:

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	[ ]	Amendment Fee	$	
	[ ]	Other Fees:		
			$	
			$	
		TOTAL:	$	

[X] A general authorization is hereby granted to charge Deposit Account No. 502807 for any fees required under 37 C.F.R. 1.16 and 1.17 in order to maintain pendency of this application.

Respectfully submitted,

ELMORE, CRAIG & VANSTONE, P.C.

By _____
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Chelmsford, Massachusetts 01863
Dated: June 28, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/888,126	Confirmation No.: 9053
Appellants	: Jennifer L. Schmitke, Donghao Chen, Richard P. Batycky, David A. Edwards and Jeffrey S. Hrkach	
Filed	: June 22, 2001	
TC/A.U.	: 1616	
Examiner	: Mina Haghighatian	
Docket No.	: 2685.2030-000	
Customer No.	: 000038421	
Title	: Particles for Inhalation Having Rapid Release Properties	

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APPEAL BRIEF

Sir:

This Brief on Appeal is submitted pursuant to the Notice of Appeal received in the U.S Patent and Trademark Office on April 28, 2005, and in support of the appeal from the final rejection(s) set forth in the Office Action mailed on January 11, 2005. The fee for filing a brief in support of an appeal is enclosed.

(1) The Real Party of Interest

The real party of interest in this appeal is Advanced Inhalation Research, Inc. by virtue of Assignment recorded on January 22, 2002 at Reel 012544 and frame 0581.

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Application No.: 09/888,126

(2) Related Appeals and Interferences

There is a related appeal in U.S. Pat App. No. 10/179,463. A notice of appeal was filed in the related application on April 14, 2005. A Brief on Appeal is being filed in the related application on even date herewith.

(3) Status of the Claims

Claims 1, 3-18, 20-39 and 41-60 are pending, finally rejected and appealed. Claims 2, 19, and 40 were previously canceled.

(4) Status of the Amendments

No amendment after final rejection has been filed. A Reply After Final Rejection was filed on March 10, 2005.

(5) Summary of the Invention

The invention relates to a novel insulin-containing formulation suitable for efficient inhalation having a controllable, in particular, a rapid, release profile. This rapid release profile provides a desirable alternative to injection therapy and particularly for the treatment of diabetes in humans. The presently claimed formulation comprising particles having, by weight, approximately 60% DPPC, approximately 30% insulin, and approximately 10% sodium citrate was chosen for its superior fast acting properties, and superior stability and manufacturability. The presently claimed formulation of the invention has numerous advantages. For example the presently claimed formulation provides a rapid release profile for abbreviated residence of insulin in the lung and decreases the amount of time in which therapeutic levels of insulin are present in the local environment or systemic circulation. The rapid release of insulin provides a desirable alternative to injection therapy currently used for treating diabetes. In addition, the invention provides a method for treating a human patient in need of insulin comprising administering the presently claimed formulation via delivery to the pulmonary system wherein the high initial release of active agent, typically seen in inhalation therapy is boosted giving very high initial and rapid release of insulin.

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Consequently, patient compliance and comfort can be increased by reducing the frequency of dosing and avoiding the necessity to inject insulin.

(6) Issues

The sole issue on appeal is whether the Examiner has established a *prima facie* case of obviousness of one or all claims.

(7) Grouping of Claims

The claims do not stand or fall together. Claims 1 and 3-17 are grouped together. Claims 18, and 20-38 are grouped together. Claims 30 and 41-58 are grouped together. Claims 59 and 60 each stand on their own. Appellants present reasons for the separate patentability of the claims in the Argument.

(8) Argument

(a) The Rejection

In the Advisory Action dated April 22, 2005, the Examiner maintains the finality of the rejection made in the Final Office Action dated January 11, 2005. In the Final Office Action, the Examiner rejects claims 1, 3-18, 20-39 and 41-60 under 35 U.S.C. 103(a) as being unpatentable over Patton et al., U.S. Patent No. 5,997,848 ("Patton") in view of Edwards et al., U.S. Patent No. 5,985,309 ("Edwards").

(b) The Rebuttal

In the Final Office Action, the Examiner relies upon Patton to teach dry powder insulin that can be administered to a mammal, resulting in a systemic delivery characterized by rapid absorption. The rejection states that the product can be prepared by dissolving insulin in an aqueous buffer (such as a citrate buffer) and spray drying the solution to produce amorphous particles having "a particle size less than 10 microns." According to the rejection, preferred carriers disclosed by Patton include amino acids, such as glycine, lysine, etc. The Examiner notes that insulin and carrier concentrations

can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. The Examiner notes, however, that Patton does not teach the use of DPPC as a carrier.

The Examiner turns to Edwards to establish that surfactants, such as DPPC, are known in the manufacture of insulin-containing inhalation products. The Examiner suggests that the person of ordinary skill in the art would be motivated to modify the formulations of Patton to use DPPC, as taught by Edwards, because DPPC was known to be a natural lung surfactant.

Even if the Examiner has established a *prima facie* case of obviousness (i.e. that it would be obvious to substitute some or all of Patton's insulin, buffer, and a carrier for Edward's DPPC), the evidence of record establishes significant unexpected results. Simply, the evidence establishes that the specific amounts of these components are critical. Thus the selection of the presently claimed approximate amounts of 60% DPPC, 30% insulin and 10% citrate combination is patentable over the myriad of possible combinations derived from the combination of Patton and Edwards. However, in the Final Office Action, the Examiner maintains the obviousness rejection even in view of Appellants' evidence of significant unexpected results in the form of a Rule 132 declaration.

In the Advisory Action, the Examiner states that the first sentence of the above-paragraph is an "agreement" on Appellants' part that it would have been obvious to have added Edward's DPPC to the insulin formulations of Patton. This is untrue.

It is well settled that unexpected results must be established by factual evidence. *In re Lindner*, 173 USPQ 356 (CCPA 1972). Appellants have provided this factual evidence in the form of a Rule 132 declaration. It is also well settled that proof of unexpected properties may be in the form of direct or indirect comparative testing of the claimed compounds and the closest prior art. *In re Payne*, 203 USPQ 245, 256 (CCPA 1979) and *In re Grasselli*, 218 USPQ 769 (CAFC 1983).

A proper showing of unexpected results will rebut a prima facie case of obviousness. *In re Fenn*, 639 F.2d 762, 208 USPQ 470 (CCPA 1981). In *In re Fenn*, the court approved the use of declaratory evidence showing an indirect comparison between

the appellant's diaphragm prepared according to appellant's specification and the swelling characteristics of the closest prior art which was sufficient to provide an indirect showing of unexpected superiority sufficient to rebut a *prima facie* case of obviousness.

In the Final Office Action, the Examiner does not appear to contest the sufficiency of Appellants' declaratory evidence or the unexpected superiority of the results provided therein other than to state that the declaratory evidence is "not found persuasive". The Examiner has instead, simply maintained the obviousness rejection without any articulated rationale or evidentiary support as to *why* Appellants' comparative data is insufficient to rebut the Examiner's obviousness objection. MPEP 2144.08 (III). On page 3 of the Final Office Action, the Examiner states that:

> "[the Declaration] was not found persuasive because while it provided data on the stability of certain concentration ranges, it did not overcome the prior art rejections. While applicant insists that the specific amounts of each ingredient makes the formulations stable, the concentration ranges fall within the ranges disclosed by the references and thus it is considered that the prior art of record meets the claimed limitations."

In the Advisory Action, the Examiner apparently attempts to contest the sufficiency of Appellants' declaratory evidence by providing additional reasons as to why the declaration is insufficient. The Examiner states that:

> "While it is accepted that Applicant's declaration shows certain properties of formulations having different ratios of DPPC:sodium citrate:insulin, it does not show significant unexpected results as Applicant claims. The figures that show different "crash out" times are not clearly showing a significant difference. Furthermore the Declaration fails to recite side by side comparisons of the instant formulations with those of the prior art and thus do not overcome the prior art rejection."

The Examiner is simply incorrect about the lack of significance of the unexpected results described in the declaration. Figure 2, for example, of Appellants' 132 declaration clearly shows that 10% insulin formulations experience rapid "crash out" of solution times ranging from 5 minutes to two hours depending upon the concentration of insulin comprising the 10% formulation. On the other hand as shown in Figure 2, the 30% insulin formulation does not crash out of solution *at all*. As discussed in the Appellants'

declaration, this result would not have been predictable based solely on DPPC solubility (see Figure 1 of the declaration) and results in a dramatic improvement in manufacturability of the formulation that could not have been predicted. In response to the Examiner's argument that Appellants did not provide side by side comparison of the instant formulations with those of the prior art, Appellants' provided comparative data with formulations that were *even closer* to Appellants' claimed formulations as is permissible and will be discussed in more detail below.

In the MPEP, 2144.05 (III) it states that "[a]pplicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range". Appellants' 132 declaration clearly shows that the criticality of the presently claimed formulation (not a *range* of formulations as described by the Examiner, but instead a superior *single species* of formulation), having particles comprising, by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate possesses unexpected properties as compared to formulations that are even *closer* than those of the combination of prior art cited by the Examiner. The Patton reference cited by the Examiner discloses that insulin and carrier concentrations can be within the broad range of 5-95%, preferably between 20-80% by weight for insulin. Patton makes no specific mention of the range of aqueous buffer. The Examiner relies on Edwards to provide DPPC as a carrier but no preferred DPPC range is disclosed in Edwards. In the Examples, Edwards describes a number of different DPPC-containing formulations, including formulations containing 10%, 33% and 60% by weight DPPC. Clearly, the combination of cited references provides so many possible combinations of formulations, that evidence of unexpected results (provided by Appellants' 132 declaration) for a *single* combination (species) of formulation necessitating the selection of three specific components in a single specific combination, within the prior art ranges cited by the Examiner is more than sufficient to overcome any *prima facie* case of obviousness in view of the combined references. For example in *In re Ruschig*, 145 USPQ 274 (CCPA 1965), the court was faced with claimed species of compounds that fell into the general class of sulfonylureas, known to be a large class of compounds. The compounds singled out for patenting had been discovered by appellants as a part of their systematic and

extensive research, to possess the ability to lower the level of blood sugar, for use in treating diabetes but also because of other desirable properties that they possess in connection with such use. Appellants provided an declaration of record indicating that as compared with compounds of similar structure to the claimed compounds, the claimed compounds are distinguishable based on a number of properties including shelf-life, handling and that they also have no bacteriostatic action as compared to similar anti-diabetic compounds. The *Ruschig* court reversed the Patent Office's obviousness rejection and citing *In re Lunsford* 140 USPQ 425, 427 stated that:

> "and in *In re Lunsford*, 51 CCPA 1000, 327 F.2d 526, 140 USPQ 425, 427, wherein Judge Martin, speaking for the court, finding an "unobvious property inherent in the claimed compounds" sufficient to overcome a showing of very close structural obviousness, said "there is no basis in law for ignoring any property," and in *In re Ward*, 51 CCPA 1132, 329 F.2d. 1021, 141 USPQ 227, 228, wherein the court said:
>
> * * * claims to chemical compounds are drawn to more than structural formulae. They define the compounds themselves and compounds possess properties which must be considered along with the formulae.
>
> Here the esters might appear to be obvious in terms of the concept of their structure but that is only half the game. There remains the consideration of the properties of the esters. * * * That unexpected property cannot be ignored in the determination of obviousness of the claimed esters *as substances* and not as structural formulae."

The case law permits patenting a species even where the prior art generically discloses it based upon evidence of unexpected results. The MPEP states that patenting within ranges is permissible with sufficient evidence of unexpected results. MPEP 716.02 (d).

Clearly, Appellants' showing of unexpected enhanced stability and manufacturability of the presently claimed *specific* formulation is sufficient to overcome any *prima facie* case of obviousness in view of the potentially infinite combinations of formulations provided by the ranges disclosed in the cited combination of Patton and Edwards. Appellants have shown unexpected and enhanced stability as compared to formulations that are even *more* similar to those of cited prior art in their 132 declaration.

With regard to the Examiner's statement in the Final Office Action that "[i]t is also noted that stability is a property of the formulations", Appellants are unclear as to

what the Examiner's point is here. If the Examiner is asserting that because stability is an inherent property of the formulations, unexpected superiority of that property is insufficient to overcome obviousness, a wealth of case law contradicts the Examiner's position.

For example in *In re Chupp*, 2 USPQ2d 1437, the Appellant (Chupp) submitted a declaration discussing the results of tests comparing the herbicidal activity of the claimed compound with that of the closest prior art compounds and with two commercial herbicides, to rebut the prima facie case of obviousness. The tests compared the compounds' ability to control two weeds and it was undisputed in the record that the claimed compound gave superior results. The board deemed the declaratory evidence insufficient to rebut the case of obviousness claiming the compound had no new or unexpected property; it possesses the same property as the prior art compounds. The court, citing *In re Papesh*, 137 USPQ 43 (CCPA 1963), stated that:

> "The Papesch court held, "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing" (citation omitted). Under the Papesch doctrine, evidence of unobvious or unexpected advantageous properties may rebut a prima facie case of obviousness based on structural similarities [citation omitted]. Such evidence may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds. E.g. *In re Lunsford*, 357 F2d 380, 148 USPQ 716 (CCPA 1966). "

The court in *In re Chupp* went on to cite another case, *In re Ackerman*, 170 USPQ 340 at 343 (CCPA 1979) for additional precedent indicating that "evidence that a compound is unexpectedly superior in one of a spectrum of common properties, as here, can be enough to rebut a prima facie case of obviousness". Although the Solicitor in *Chupp* tried to argue that *Chupp*'s declaratory evidence did not show an unexpected difference in the properties in view of the prior art, the court disagreed. The court noted that the record did not support the Solicitor's assertion that the claimed compound's superior properties would have been expected, and to support the court's position, the court cited *In re Blondel*, 499 F2d 1311,182 USPQ 294 (CCPA 1974) (reversing rejection of claims to compounds which prior art suggested would have longer lasting pharmacological activity, where actual increase was beyond reasonable expectations).

Similarly, in the present application, the Examiner has provided no evidence that the superiority of the stability properties of the claimed formulation as described in Appellants' 132 declaration are in any way predicted or suggested in the cited combination of prior art. Neither reference discusses the criticality of the amounts of each component of the formulation to provide superior stability and manufacturability.

Perhaps the Examiner is concerned by the fact that the evidence of record compares, not the specific formulations of Patton, but more relevant or closer formulations provided by Appellants. The courts have looked favorably upon indirect evidence that is even closer than that of the prior art. For example, in *In re Grasselli*, *supra*, an applicant claiming a catalyst showed unexpected results when he tested the claimed catalyst with the most similar catalysts, which were his own, that were claimed in broader claims. The court found that none of the prior art cited by the examiner described a catalyst more similar to the claimed catalyst than the Appellants' own catalysts claimed in the broader claims. See 218 USPQ at 779. The *Grasselli* court found this indirect showing of superiority over the prior art sufficient to rebut the Examiner's showing of obviousness.

Similarly, in the present application, neither Patton nor Edwards cited by the Examiner, provides an example of a formulation comprising all the components of the presently claimed formulation, i.e. DPPC, insulin and sodium citrate. Appellants have instead provided formulations for comparison that are *closer* than those of the cited combination of prior art. The Declaration shows that six formulations that differ solely in the relevant amounts of the hydrophobic component (e.g., DPPC), citrate and insulin can have substantial differences in stability and manufacturability. Notably, increasing the amount of insulin in the formulation from 10% to 30%, with a corresponding decrease in the lipid (i.e. "hydrophobic") component, DPPC, dramatically and unexpectedly improved the solubility of the total solids in the spray drying solution. The improved solubility of total solids is critical to the stability, manufacturability and ultimately, the desired performance of the formulation. Therefore, Appellants have met the burden of providing comparative data with the closest prior art by making an indirect showing of

unexpected superiority using prior art that is even closer than the prior art provided by the Examiner.

In view of the above arguments and citation of case law, Appellants submit that they have provided evidence in the form of a 132 declaration sufficient to meet their burden of establishing unexpected and significant properties of the presently claimed formulation. Thereby, Appellants submit that they have rebutted any *prima facie* case of obviousness that the Examiner may have established by the combination of cited references and respectfully request that the rejection under 35 U.S.C. §103 over Patton in view of Edwards be withdrawn.

Although Appellants' remarks above are limited to Appellants' evidence for rebutting a prima facie case of obviousness over Patton in view of Edwards, Appellants continue to maintain that the Examiner has not in fact established a *prima facie* case of obviousness for all of the reasons of record so far in this application. However, in order to reduce the number of issues on appeal, Appellants' position is that Appellants' declaratory evidence showing unexpected results overcomes any *prima facie* case of obviousness that Examiner may have established.

(c) Terminal Disclaimer

A terminal disclaimer was previously filed by Appellants with the Reply to the Final Rejection dated March 10, 2005, thereby obviating the obviousness-type double patenting rejection over copending Serial No. 10/179,463 in view of Patton. The Examiner does not indicate in the Advisory Action that the terminal disclaimer has been entered in the application and the Examiner does not explicitly withdraw the double patenting rejection. Appellants believe that the double patenting rejection will be withdrawn upon entry of the terminal disclaimer in the application, however it is mentioned in this Appeal Brief for thoroughness.

(d) Claim Groupings

If the Examiner finds Claim 1 allowable, then all claims are allowable as uses of a novel particle formulation and all claims dependent thereon. Even if Claim 1 is not

allowable, Claim 18 is separately allowable because claim 18 recites that the formulation is administered to the patient in a single, breath-actuated step. Such method of administration is not disclosed by Patton or Edwards and it is not made obvious by either Patton or Edwards as it is the unique characteristics of the particle formulation of the invention that makes it possible to deliver the particles in a single breath-actuated step. If claim 18 is allowable, then claims 20-38 are allowable.

If Claim 1 is not allowable, Claim 39 is separately allowable because Claim 39 recites rapid release of insulin upon simultaneous inhalation and dispersion of the particles from a receptacle containing the particles. Neither Patton nor Edwards disclose or make obvious this feature which is unique to the presently claimed particle formulation. If Claim 39 is allowable, then claims 41-57 are allowable.

If Claim 1 and 18 are allowable, then Claim 59 and 60 are allowable. Even if Claim 1 and 18 are not allowable, Claims 59 and 60 are separately allowable because neither Edwards nor Patton disclose or make obvious the use of low transition temperature phospholipids in the particle formulations of the present invention.

(e) Summary

Appellantss declaration providing unexpected results overcomes the Examiner's rejection of the claims as being *prima facie* obvious over Patton in view of Edwards. The Examiner has not provided any scientifically *accurate* evidence or rationale for claiming that Appellants' declaration is insufficient.

(9) Conclusion

Appellants request reversal of the rejection and allowance of the application.

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Respectfully submitted,

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Chelmsford, MA 01863
Dated: June 28, 2005

Application No.: 09/888,126

(8) CLAIMS INDEX

Claims as of 4/20/04

1. (original) A formulation having particles comprising, by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate.

2. canceled.

3. (previously amended) The formulation of Claim 1, wherein the particles comprise a mass of from about 1.5 mg to about 20 mg of insulin.

4. (previously amended) The formulation of Claim 1, wherein the particles are placed in a receptacle and comprise a mass of about 1.5 mg of insulin per receptacle.

5. (previously amended) The formulation of Claim 1, wherein the particles are placed in a receptacle and comprise a mass of about 5 mg of insulin per receptacle.

6. (original) The formulation of Claim 1, wherein the particles comprise a dosage of insulin of between about 42 IU and about 540 IU.

7. (original) The formulation of Claim 6, wherein the particles comprises a dosage of insulin of about 42 IU.

8. (original) The formulation of Claim 6, wherein the particles comprise a dosage of insulin of between about 84 IU and about 294 IU.

9. (original) The formulation of Claim 8, wherein the particles comprise a dosage of insulin of between about 155 IU and about 170 IU.

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10. (original) The formulation of Claim 1, wherein the particles have a tap density less than about 0.4 g/cm^3.

11. (original) The formulation of Claim 10, wherein the particles have a tap density less than about 0.1 g/cm^3.

12. (previously amended) The formulation of Claim 1, wherein the particles have a median geometric diamcter of from between about 5 micrometers to about 30 micrometers.

13. (original) The formulation of Claim 1, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 5 micrometers.

14. (previously amended) The formulation of Claim 13, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 3 micrometers.

15. (original) The formulation of Claim 13, wherein the particles have an aerodynamic diameter of from about 3 micrometers to about 5 micrometers.

16. (original) The formulation of Claim 1, wherein the particles further comprise an amino acid.

17. (original) The formulation of Claim 16, wherein the amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

18. (original) A method for treating a human patient in need of insulin comprising administering pulmonarily to the respiratory tract of a patient in necd of treatment, in a single, breath actuated step an effective amount of particles comprising by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate, wherein release of the insulin is rapid.

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19. canceled.

20. (original) The method of claim 18, wherein the patient in need of treatment has diabetes mellitus.

21. (previously amended) The method of Claim 18, wherein the particles have a mass of from about 1.5 mg to about 20 mg of insulin.

22. (original) The method of Claim 18, wherein the particles comprise a mass of about 1.5 mg of insulin per receptacle.

23. (previously amended) The method of Claim 18, wherein the particles are placed in a receptacle and comprise a mass of about 5 mg of insulin per receptacle.

24. (previously amended) The method of Claim 18, wherein the particles are placed in a receptacle and comprise a dosage of insulin of between about 42 IU and about 540 IU.

25. (original) The method of Claim 24, wherein the particles comprises a dosage of insulin of about 42 IU.

26. (original) The method of Claim 24, wherein the particles comprise a dosage of insulin of between about 84 IU and about 294 IU.

27. (original) The method of Claim 26, wherein the particles comprise a dosage of insulin of between about 155 IU and about 170 IU.

28. (original) The method of Claim 18, wherein the particles have a tap density less than about 0.4 g/cm^3.

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29. (original) The method of Claim 28, wherein the particles have a tap density less than about 0.1 g/cm^3.

30. (previously amended) The method of Claim 18, wherein the particles have a median geometric diameter from about 5 micrometers to about 30 micrometers.

31. (original) The method of Claim 18, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 5 micrometers.

32. (previously amended) The method of Claim 31, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 3 micrometers.

33. (original) The method of Claim 31, wherein the particles have an aerodynamic diameter of from about 3 micrometers to about 5 micrometers.

34. (original) The method of Claim 18, wherein administering the particles pulmonarily includes delivery of the particles to the deep lung.

35. (original) The method of Claim 18, wherein administering the particles pulmonarily includes delivery of the particles to the central airways.

36. (previously amended) The method of Claim 18, wherein administering the particles pulmonarily includes delivery of the particles to the upper airways.

37. (original) The method of Claim 18, wherein the particles further comprise an amino acid.

38. (original) The method of Claim 37, wherein the amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

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39. (original) A method of delivering an effective amount of insulin to the pulmonary system, comprising:

a) providing a mass of particles comprising by weight, approximately 60% DPPC, approximately 30% insulin and approximately 10% sodium citrate; and

b) administering via simultaneous dispersion and inhalation the particles, from a receptacle having the mass of the particles, to a human subject's respiratory tract, wherein release of the insulin is rapid.

40. canceled.

41. (previously amended) The method of Claim 39, wherein the mass of particles is from about 1.5 mg to about 20 mg of insulin.

42. (previously amended) The method of Claim 39, wherein the particles are placed in a receptacle and the mass of said particles comprises about 1.5 mg of insulin per receptacle.

43. (previously amended) The method of Claim 39, wherein the particles are placed in a receptacle and the mass of said particles comprises about 5 mg of insulin per receptacle.

44. (original) The method of Claim 39, wherein the mass of particles comprises a dosage of insulin of between about 42 IU and about 540 IU.

45. (original) The method of Claim 44, wherein the mass of particles comprises a dosage of insulin of about 42 IU.

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46. (original) The method of Claim 44, wherein the mass of particles comprises a dosage of insulin of between about 84 IU and about 294 IU.

47. (original) The method of Claim 46, wherein the mass of particles comprises a dosage of insulin of between 155 IU and about 170 IU.

48. (original) The method of Claim 39, wherein the particles have a tap density less than about 0.4 g/cm^3.

49. (original) The method of Claim 48, wherein the particles have a tap density less than about 0.1 g/cm^3.

50. (previously amended) The method of Claim 39, wherein the particles have a median geometric diameter of from about 5 micrometers to about 30 micrometers.

51. (original) The method of Claim 39, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 5 micrometers.

52. (original) The method of Claim 50, wherein the particles have an aerodynamic diameter of from about 1 micrometer to about 3 micrometers.

53. (original) The method of Claim 50, wherein the particles have an aerodynamic diameter of from about 3 micrometers to about 5 micrometers.

54. (original) The method of Claim 39, wherein delivery to the pulmonary system includes delivery to the deep lung.

55. (original) The method of Claim 39, wherein delivery to the pulmonary system includes delivery to the central airways.

56. (original) The method of Claim 39, wherein delivery to the pulmonary system includes delivery to the upper airways.

57. (original) The method of Claim 39, wherein the particles further comprise an amino acid.

58. (original) The method of Claim 57, wherein the amino acid is leucine, isoleucine, alanine, valine, phenylalanine or any combination thereof.

59. (original) The formulation of Claim 1, wherein the particles further comprise a low transition temperature phospholipid.

60. (original) The method of Claim 18, wherein the particles further comprise a low transition temperature phospholipid.

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(9) EVIDENCE APPENDIX

1.132 Declaration of Jennifer L. Schmitke (attached)